REMARKS

Status of the claims

Claims 1 and 36-43 are hereby canceled to expedite prosecution (claims 2-35 were previously canceled); claims 44, 46-53, 55-62, and 64-70 are hereby amended, and claims 71-76 are hereby added. As such, claims 44-76 are currently pending.

The canceled and amended claims have been canceled or amended, respectively, without prejudice or disclaimer, and Applicants reserve the right to pursue any subject matter encompassed in the canceled claims, or in the amended claims prior to their amendment, in subsequent continuation or divisional applications.

No new matter has been added by this amendment, and its entry is respectfully requested. The amendment to claim 44 to recite 'G' and the amendment to claim 53 to recite 'A' (as well as the analogous amendment to claim 62) merely explicitly recites the complements of the 'C' and 'T' nucleotides, respectively. Support for saliva and buccal cells as biological samples (as recited in the amendments to claims 49, 58, and 67) is found at, for example, page 48 (lines 19-20) of the specification. The amendments to claims 47-48, 50-52, 56-57, 59-61, 65-66, and 68-70 are made merely to maintain proper antecedent basis, and for consistency and clarity of language.

This amendment adds, changes, and/or deletes claims in the instant application. A detailed claim listing is presented above with appropriate status identifiers for each claim, in accordance with 37 C.F.R. §1.121(c).

Rejections under 35 USC §112, first paragraph, enablement

Claims 1 and 36-70 are rejected under 35 USC §112, first paragraph, for allegedly being not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully traverse.

As an initial matter with respect to this enablement rejection, it is unclear why the Patent Office has maintained (in the Final Office Action of December 10, 2007, hereinafter "FOA") its assertions that the specification does not provide guidance for detecting a SEQ ID NO:7368 SNP in "any" individual (only humans), and the specification does not provide guidance for detecting any SNP within SEQ ID NO:7368 (the specification teaches a single SNP location in SEQ ID

NO:7368 at position 101), because amendments were made in Applicant's submission of April 6, 2007 that amended claim 1 to recite "human" (rather than "individual") and to specify position 101 of SEQ ID NO:7368 (and the other pending claims are also drawn to humans, and to position 101 of SEQ ID NO:7368), thereby clearly obviating these aspects of the enablement rejection.

Regarding the Patent Office's assertion that the specification and claims do not set forth what the increased risk is or decreased risk is relative to, this was addressed by Applicants in the Submission Accompanying Pre-Appeal Brief Request, filed April 10, 2008. The Odds Ratios (OR) for the 'C' allele of hCV8227677 (the SNP at position 101 of SEQ ID NO:7368) are greater than one, as shown in Tables 6-7 of the instant application, thus indicating that the 'C' allele is associated with an increased risk of Alzheimer's disease (and is therefore considered the "risk" allele). Furthermore, as also shown in Tables 6-7, the 'C' allele is over-represented in cases as compared to controls (see columns labeled "Case Allele 1 Freq" and "Control Allele 1 Freq" in Tables 6-7). Consequently, the 'T' allele is thereby associated with a decreased risk of Alzheimer's disease *relative to the 'C' allele* (and the 'T' allele is therefore considered the "non-risk" or "protective" allele). Thus, the increased and decreased risk for Alzheimer's disease associated with each allele is relative to the risk associated with the other allele.

With respect to the references cited by the Examiner, Applicants agree that the art acknowledges that associations of genetic variations with disease may be irreproducible. Accordingly, to ensure that the association of SNP hCV8227677 with Alzheimer's disease *is* reproducible, Applicants have undertaken a rigorous process of genotyping and analysis, while adjusting for potentially confounding factors (*e.g.*, APOE genotype, age, and gender), in independent sample sets in order to replicate initial findings. In particular, the association of SNP hCV8227677 with Alzheimer's disease is *not* based on an association observed only in a single study, but rather is based on replication of the association in multiple independent studies.

For example, as stated on page 20, lines 25-29, "Table 6 provides results of markers that are significant in at least two independently collected sample sets, which further verifies the association of these SNPs with Alzheimer's disease. Table 7 lists an additional set of markers that have shown significant association in one sample set ($p<0.05$) and remain significant ($p<0.01$) after all genotyped sample sets, including the initial set, are analyzed together".

Also, as stated on page 119, lines 8-17, "the association of a marker with Alzheimer's disease was considered replicated if the marker exhibits an allelic or genotypic association test p-

value <0.05 in one of the sample sets and the same test and strata are significant (p<0.05) in either one or two other independent sample sets, or the Cochran-Mantel-Haenszel p-value was significant (p<0.05) for the combined data of the other two sample sets for the same test and strata. SNPs that fall in this category are listed in Table 6. SNP-strata combinations that are not listed in Table 6, but were significant in one sample set (p<0.05) with the allelic or genotypic association test and the Cochran-Mantel-Haenzsel test was significant (p<0.01) with the same test and same strata when all available sample set data were analyzed together, are listed in Table 7."

SNP hCV8227677 is included in both of Tables 6 and 7 and thus SNP hCV8227677 met all these criteria for significance.

For example, as specifically recited on page 119 (line 18) through page 120 (line 6) of the specification, "an example of a replicated marker, where the minor allele is associated with increased risk for Alzheimer's disease is hCV8227677 (Table 6). hCV8227677 shows significant association with all individuals (strata = "ALL") of sample set 1 and the "ALL" strata of the jointly analyzed sample sets 2 & 3. In addition, the female ("male=0"), the APOE4 present ("apoe4=1"), and both age of onset substrata ("age_ge75=0", "age_ge75=1") are significantly associated for this marker in 2 independent, non overlapping sample sets. The "ALL" strata for sample set 1 shows significant Cochran-Mantel-Haenszel p-values (corrected for APOE4 status, gender, and age of disease onset) in the allelic (p=0.00601), the additive genotypic (p=0.00587), and the recessive genotypic tests (p=0.00001). The dominant genotypic test is not significant (p=0.9775). The "ALL" strata of the combined sample sets 2 and 3 confirm the sample set 1 results with significant Cochran-Mantel-Haenszel test p-values (corrected for sample set, APOE4 status, gender, and age of disease onset) in the allelic (p=0.00016), additive genotypic (p=0.00017), and the recessive genotypic test (p=0.00324). The allelic and recessive odds ratios for hCV8227677 show similar effects in these sample sets, indicating the C-allele as risk factor, and thereby further strengthening the association of this marker with Alzheimer's disease (sample set 1: OR allelic=1.37 (95%CI=1.09-1.71), OR recessive=2.35 (95%CI=1.61-3.43); sample sets 2 and 3 combined: OR allelic=1.41 (95%CI=1.18-1.69), OR recessive=1.59 (95%CI=1.17-2.16)). The odds ratios are based on the minor allele as observed in the control samples (i.e. C-allele for hCV8227677)."

With respect to the *Hirschhorn* reference in particular, the Examiner cites *Hirschhorn* in supporting the rejection for lack of enablement, stating that Hirschhorn "teaches that most reported associations are not robust" (FOA, page 3). However, this argument does not support the allegation that the instant invention is not reliable. The mere fact that other association studies were not easily reproduced does not cast doubt on the enablement of the instantly claimed invention. As taught in *Hirschhorn*, many factors could cause the other studies to fail, factors that are not present in the instant studies. Moreover, the *Hirschhorn* reference is not particularly applicable to the reliability of the association of SNP hCV8227677 with Alzheimer's disease because the Examiner states that "*Hirschhorn* cautions in drawing conclusions from a *single* report of an association between a genetic variant and disease susceptibility" (FOA, page 4, emphasis added). However, in the instant situation, the association of SNP hCV8227677 with Alzheimer's disease has been replicated in more than a single study – specifically, the association of SNP hCV8227677 with Alzheimer's disease has been replicated in *four* large, well-characterized case-control samples. See Grupe *et al*, *American Journal of Human Genetics*, Vol. 79, at page 183.

With respect to the *Ioannidis* reference in particular, the Examiner cites *Ioannidis* in supporting the rejection for lack of enablement, stating that "the results of the first study correlate only modestly with subsequent research on the same association" (FOA, page 4). Again, however, this reference is not particularly applicable to the reliability of the association of SNP hCV8227677 with Alzheimer's disease because the association of SNP hCV8227677 with Alzheimer's disease has been replicated in more than one sample – specifically, the association of SNP hCV8227677 with Alzheimer's disease has been replicated in *four* studies. See Grupe *et al*, *American Journal of Human Genetics*, Vol. 79, at page 183.

With respect to the *Bertram* reference in particular, the Examiner doubts the reliability of the instant invention by citing *Bertram* because Bertram failed to replicate the instant study in the two samples that they tested. In a response to Bertram, Grupe *et al.* presented sound scientific reasoning pointing out the deficiencies in the Bertram study, such as the difference between family-based samples and case-control samples, inadequacies of the characterization of controls in Bertram, etc. See Grupe *et al*, *American Journal of Human Genetics*, Vol. 79, at page 183. Grupe *et al.* concluded that Bertram's failure to "replicate our results does not necessarily

indicate that the original association was a false-positive result" (Grupe *et al*, *American Journal of Human Genetics*, Vol. 79, at page 184).

Applicants have alluded to this reasoning in the previous response to office action, but that reasoning was dismissed as "attorney argument" (FOA, at page 7). It is important to note that, contrary to the Examiner's assertion that Applicants' analysis of the discrepancies between Bertram and the instant invention are mere "attorney arguments that cannot replace evidence on the record" (FOA, page 7), these discrepancies are evidence on the record as they are published in peer-reviewed journals, and cited in the office actions.

Accordingly, it is respectfully requested that the rejections under 35 USC §112, first paragraph, for allegedly lack of enablement be reconsidered and withdrawn.

Rejection under 35 USC §112, first paragraph, written description (new matter)

Claim 64 was rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. The Examiner stated that this is a rejection for new matter, and the Examiner could not find any basis in the specification that teaches that SEQ ID NO:7368 is within the LRP2 gene as represented by SEQ ID NO:6756.

To expedite prosecution, claim 64 is hereby amended to indicate that SEQ ID NO:7368 is contained within the genomic sequence of SEQ ID NO:6756. It is clear in Table 2 that SEQ ID NO:7368, which is a context sequence of 201 nucleotides surrounding the SNP of hCV8227677 (hCV26838632), is contained with the genomic sequence of SEQ ID NO:6756.

Additionally, claims 46 and 55 are hereby amended merely for consistency with amended claim 64.

Conclusions

In light of the amendments and remarks in the present and the previous responses, Applicants submit that the present application is fully in condition for allowance.

The Examiner is invited to contact the undersigned via telephone if a phone interview would expedite the prosecution of the instant patent application.

Respectfully submitted,

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